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PPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/493,353	LINNEN ET AL.	
	Examiner	Art Unit	
	Jeanine A Enewold Goldberg	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed March 12, 2001. Currently, claims 1-64 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection.

Priority

4. This application claims priority to 60/118,497, filed February 3, 1999.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claim 42 is rejected under 35 U.S.C. 102(b) as being anticipated by Han (PNAS, Vol. 88, pg. 1711-1715, 1991).

This rejection is drawn to the broadly drawn claim which requires that SEQ ID NO: 11, 12 and 13 be embedded in a larger sequence.

Han teaches the 5' UTR region of which comprises SEQ ID NO: 11, 12 and 13. SEQ ID NO: 11 is located at nucleotide positions 95-122 of the Han 5' UTR sequence. Additionally, SEQ ID NO: 12 is located at nucleotide positions 252-279. Finally, SEQ ID NO: 13 is located at nucleotide positions 254-279. Thus, Han has taught every limitation of the claimed invention.

Response to Arguments

The response traverses the rejection. The response asserts that the claims are now drawn to oligonucleotide probes comprising SEQ ID NO: 11-13. This argument has been reviewed but is not convincing because the addition of the term oligonucleotide does not provide any structural or length limitations. Further, the specification is silent on a specific definition of oligonucleotide. The nucleic acids of Han encompasses the entire 5' UTR region which itself may be potentially used as a probe. Thus for the reasons above and those already of record, the rejection is maintained.

6. Claim 42 is rejected under 35 U.S.C. 102(b) as being anticipated by Kolykhalov et al (J. of Virology, Vol. 70, No. 6, pg. 3363-3371, June 1996).

This rejection is drawn to the broadly drawn claim which requires that SEQ ID NO: 14 and 15 be embedded in a larger sequence.

Kolykhalov teaches the 3' UTR region of which comprises SEQ ID NO: 14 and 15. SEQ ID NO: 14 is located at nucleotide positions 9450-9474 of the Kolykhalov 3' UTR sequence. Additionally, SEQ ID NO: 15 is located at nucleotide positions 9452-9476. Thus, Kolykhalov has taught every limitation of the claimed invention.

Response to Arguments

The response traverses the rejection. The response asserts that the claims are now drawn to oligonucleotide probes comprising SEQ ID NO: 14-15. This argument has been reviewed but is not convincing because the addition of the term oligonucleotide does not provide any structural or length limitations. Further, the specification is silent on a specific definition of oligonucleotide. The nucleic acids of Kolykalov encompasses the entire 3' UTR region which itself may be potentially used as a probe. The 3' UTR region is only 98 nucleotides in length which is well within the range of probes. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3-13, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991).

The rejection of Claim 42 is directed to a narrow embodiment such that if the claim were amended to recite consisting of language.

Han et al. (herein referred to as Han) teaches the sequence of 341 base pairs from the 5' untranslated region (UTR) of HCV and alignment of this sequence from several different HCV isolates. Han teaches extracting the plasma from HCV-positive or negative blood donors. RNA was isolated and converted into single-stranded cDNA by reverse trancriptase using the appropriate cDNA primer (pg 1711, col 2). Han teaches primers for the PCR amplification of 5' UTR and means of cloning these PCR products (pg. 1711, col. 2, and Figure 2). The PCR products were analyzed by southern blot hybridization using a labeled oligonucleotide probe (pg 1711, col 2). Han teaches that when the sequence of the 5' UTR is compared among isolates, there is a high degree of sequence homology and that the sequence mismatches that are present are clustered in 5 positions, as taught in Figure 2 (see also pg. 1713, para 1). Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4). Han teaches Primer 51 was used to primer cDNA synthesis on HCV RNA extracted from plasma (pg 1712, col. 1). Primer 51 is located from position 268-251 (Figure 2). Moreover, Han teaches primers 52, 11, 95 and probes 89 and 90a. Primer 95 overlaps SEQ ID NO: 1, CAGAAAGCGTCTAG are in common.

Han does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 5' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Han to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Han. Since Han provides an alignment of several isolates which show conserved regions between the isolates, and delineates the ORFs, the ordinary artisan would have been motivated to have designed primers which amplify various regions of interest from the 5' UTR region. Specifically, the skilled artisan would have picked SEQ ID NO: 1 and 4 to have amplified the ORF2 and would have chosen SEQ ID NO: 2 and 7, SEQ ID

NO: 3 and 5 or SEQ ID NO: 3 and 6 which flank ORF3. Furthermore, the skilled artisan would have chosen SEQ ID NO: 11, 12 or 13 for probing the detection of HCV. The ordinary artisan would have been motivated to amplify the 5' UTR region of HCV since Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose. Thus, any primers which amplify the 5' UTR region and any probes within the 5' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The response asserts that Han reference does not provide oligonucleotide sequences for any particular probe or primer for this 5' UTR, let alone the particular oligonucleotide sequences of the instant invention. This argument appears directed to a reason why Han is not a 102 reference. This argument has been reviewed but is not convincing because Han has taught four primers which amplify 5' UTR and two probes for this region. Han teaches Primer 51 was used to prime cDNA synthesis on HCV RNA extracted from plasma (pg 1712, col. 1). Primer 51 is located from position 268-251 (Figure 2). Moreover, Han teaches primers 52, 11, 95 and probes 89 and 90a. Primer 95 overlaps SEQ ID NO: 1, i.e., the seqeucne CAGAAAGCGTCTAG is in common.

The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in

Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides the teaching "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection.

The response asserts that the primers/probes of the instant invention are of "superior sensitivity when compared to the Roche AMPLICOR assay". The response appears to be trying to argue unexpected results. This argument has been reviewed but is not convincing because the instant primer pairs have been compared to a single assay, namely the Roche AMPLICOR assay. This is only one of the numerous assays which have been taught in the art. Other assays which amplify the HCV region have been taught, including those of record. Comparison of the instant primer pairs to a single assay does not yield unexpected results since the instant primers have not been compared to a representative number of primer pairs. With regards to the results of the comparison assays of Table 3-6, the primer pairs of SEQ ID NO: 2 and 7, SEQ ID NO: 1 and 4, SEQ ID NO: 3 and 5, SEQ ID NO: 3 and 6 were compared. The level of skill in the art with regard to the amplification of the 5' UTR region of HCV with different probes

and primers is very high. To demonstrate that the instant primers/ primer pairs are have unexpected results, the detection would need to demonstrate superior results to more than a single set of primers.

Moreover, a detailed look at the primer pairs of the instant application and those of Roche illustrate that KY78 is similar and overlapping with SEQ ID NO: 5, 6, and 7. KY78 overlaps with SEQ ID NO: 5. Nucleotides 4-24 of KY78 are identical to nucleotides 1-21 of SEQ ID NO: 5. KY78 overlaps with SEQ ID NO: 6. Nucleotides 1-24 of KY78 are identical to nucleotides 3-26 of SEQ ID NO: 6. KY78 overlaps with SEQ ID NO: 7. Nucleotides 1-22 of KY78 are identical to nucleotides 8-25 of SEQ ID NO: 7.

Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 43, 45, 47, 49-50, 54, 56, 58, 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) as applied to Claim 1, 3-13, 40-42 above, and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Han does not specifically teach packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Han with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The

ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Han into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Han's deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers taught by Han included, into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

9. Claims 14, 16-26, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996).

The rejection of Claim 42 is directed to a narrow embodiment such that if the claim were amended to recite consisting of language.

Kolykhalov et al. (herein referred to as Kolykhalov) teaches a highly conserved sequence at the 3' terminus of the HCV genome RNA. Kolykhalov teaches preparing HCV RNA from human serum (pg 3363, col 2)(limitations of Claim 21). Kolykhalov

teaches using nested primer pairs corresponding to a region in the 5'NTR for RNA isolation (pg 3363, col 2). Furthermore, Kolykhalov teaches using primer pairs specific for the novel 98-base element at the 3' end of the HCV genome to analyze for the presence of novel sequences (pg 3364, col 1)(limitations of claim 16). PCR products were analyzed by electrophoresis on a polyacrylamide gel (limitations of Claim 14, 17, 18). Kolykhalov teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. The region is also found at the 3' termini of several independent HCV isolates which is highly conserved with between 98-100% sequence identity for the examined isolates. Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV replication and recovery of infectious HCV RNA from cDNA, the apparent conservation of the 3' element may have important applications for HCV diagnosis and therapy"(pg 3370, col 2).

Kolykhalov does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 3' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Kolykhalov to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 3' UTR region to detect HCV, as taught by Kolykhalov. Since Kolykhalov provides an alignment of several isolates which show conserved regions between the isolates (Figure 3), the ordinary artisan would have been motivated to have designed primers which amplify the 98-nucleotide conserved region from the 3' UTR region. Specifically, the skilled artisan would have picked primers from the 5' and the 3' end of the 98-nucleotide conserved region of the 3' UTR which were conserved among the isolates, for example SEQ ID NO: 8 and SEQ ID NO: 9. Furthermore, the skilled artisan would have probed the sequence with a probe such as SEQ ID NO: 14 or 15 which would detect the specific isolates desired. The ordinary artisan would have been motivated to amplify the 3' UTR region of HCV since Kolykhalov teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. Additionally, Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV replication and recovery of infectious HCV RNA from cDNA, the apparent conservation of the 3' element may have important applications for HCV diagnosis and therapy". Thus, any primers which amplify the 98-nucleotide

conserved region of the 3' UTR region and any probes within this 3' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides the teaching "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection.

The response asserts that the primers/probes of the instant invention are compared to the ROCHE assay and another PCR assay "Rochester General Hospital 5' NCR nested PCR assay". The response asserts that the detection system of the present invention is both sensitive and specific when compared to the other PCR systems. This argument has been reviewed but is not convincing because the instant

application has demonstrated that the 3' primers detect HCV when compared with other 5' primers such that this is not a relevant comparison. The response has not addressed the "unexpected" results of the instant primers to those of the reference, namely Kolykhalov.

Thus for the reasons above and those already of record, the rejection is maintained.

10. Claims 51-53 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996) as applied to Claims 14, 16-26, 40-42 above, and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Kolykhalov does not specifically teach packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Kolykhalov with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Kolykhalov into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Kolykhalov's deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers included, into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

11. Claims 14, 16-26, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998).

Tanaka et al. (herein referred to as Tanaka) teaches the 3' UTR region of HCV. As seen in Table 2, numerous primers and a probe for this region are taught. Tanaka also teaches analysis of clinical samples (col 8). RNA was prepared from serum and reverse transcription was carried out using specific primers (col. 8, lines 18-22)(limitations of Claim 16, 17, 21). The cDNA synthesized was mixed with primers, and the PCR product was detected upon agarose electrophoresis (col 11, lines 10-16)(limitations of Claim 18, 24). A southern blot was also used for conformation (limitations of Claim 19, 25). A probe R3 was used for detection (col 11).

Additionally, Encke et al. (herein referred to as Encke) teaches "recently, a highly conserved, 98 nucleotide long sequence at the very 3' end of the HCV genome which is

the third region has been described and appears to play an important role in viral replication and possible infectivity (pg 118, col 1).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Tanaka and the teachings of Encke to obtain the claimed invention as a whole. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural homologues of the full length disclosed 3' UTR of the HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. The skilled artisan would have been motivated to have used primers from the 3' UTR region to detect HCV, as taught by Tanaka, for the express benefit of detecting a "recently, a highly conserved, 98 nucleotide long sequence at the very 3' end of the HCV genome which is the third region has been described and appears to play an important role in viral replication and possible infectivity, as taught by Encke . Since Tanaka teaches the 3' UTR sequence and the 98

nucleotide conserved region, the skilled artisan would have designed primers within this 98 nucleotide region for the express benefit of detection of HCV. Thus, any primers which amplify the 3' UTR region would have been obvious.

Response to Arguments

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides "to maximize the probability that a given primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection.

The response asserts that "at best, given what is taught in Tanaka and Encke a skilled artisan might only be motivated to try various probes and primers designed from the 3'-UTR taugth in those references". This argument has been reviewed but is not convincing because optimization of primers and primer pairs is routine in the art. The

art teaches how to alter the conditions to obtain primer/primer pairs which amplify the target.

Thus for the reasons above and those already of record, the rejection is maintained.

12. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998) as applied to Claims 14, 16-26, 40-42 above, and further in view of Maertens et al (US Pat. 5,846,704, December 1998).

Neither Tanaka nor Encke specifically teach performing reverse transcriptase with random oligonucleotide primers.

However, Maertens et al teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68)(limitations of Claim 8). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68)(limitations of Claim 2). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the extraction method of Tanaka with the extraction method of Maertens to obtain the claimed invention as a whole. The ordinary artisan would have realized that RNA may be transcribed using either random primers, as taught by Maertens, or primers corresponding to specific

HCV RNA, as taught by Tanaka. Since the art teaches that RNA from HCV may be reverse transcribed using either random or specific primers, the ordinary artisan would have realized that they were equivalents and may have substituted random primers for primers corresponding to specific HCV regions.

Response to Arguments

The response traverses the rejection. The response asserts that Maertens does not teach or suggest any of the particular nucleic acid probes and primers of the invention. This argument has been reviewed but is not convincing because as argued above, Taqnaka or Encke both teach the 3' UTR region which is only 98 nucleotides in length, and primer design, absent secondary considerations is obvious. Thus for the reasons above and those already of record, the rejection is maintained.

13. Claims 27-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Maertens et al (US Pat. 5,846,704, December 1998) or Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) as applied to Claims 1, 3-13, 40-42 above, in view of either Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996) as applied to Claims 14, 16-26, 40-42 above or Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998) as applied to Claims 14, 16-26, 40-42 above.

Maertens et al. teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches primers which have at least 15 contiguous nucleotides from SEQ ID NO: 3 and 4. The

inner primers of Maertens denoted as SEQ ID NO: 3 and 4 which overlap at least 15 contiguous nucleotides of the instant SEQ ID NO: 3 and 5/6. Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68)(limitations of Claim 8). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68)(limitations of Claim 2). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10). The PCR product was then subjected to electrophoresis in an agarose gel and ethidium bromide staining (col. 25, lines 14-15)(limitations of Claim 4, 5, 11). Furthermore, strips of immobilized HCV-specific primers developed and hybridized with PCR amplified DNA fragments of the 5' UTR for visualization (col. 25, lines 50-60)(limitations of Claim 6, 12). As claimed in Maertens Claim 11, the inner primers of the reaction are required to hybridized to SEQ ID NO: 3 and 4. The instant primers of SEQ ID NO: 3, 5 and 6, would hybridize to SEQ ID NO: 3 and 4 of Maertens in addition to satisfying the teachings that the primers have at least 15 contiguous nucleotides from SEQ ID NO 3 and 4 (limitations of Claim 1, 9-10). Maertens teaches a kit which comprises a set of primers, a set of probes immobilized on a solid substrate, and buffers (col. 20, lines 45-55)(limitations of Claim 43, 45, 54, 56). Thus, Maertens has taught every limitation of the claimed invention.

Neither Maertens nor Han nor Kolykhalov nor Tanaka nor Encke specifically teach a method which combines amplifying both the 5' UTR region and the 3' UTR region for detection of HCV.

However, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Maertens or Han with the teachings of Kolykhalov or Tanaka and Encke to obtain the claimed invention as a whole. The ordinary artisan would have combined the teachings of Maertens or Han with the teachings of Kolykhalov or Tanaka and Encke to generate a more complete and versatile assay for the detection of HCV which encompassed both the 5' UTR region and the 98-base sequence of the 3' UTR region. The art, Han, teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4). The art, Kolykhalov, teaches that the 98-base nonhomopolymeric sequences is not present in human genomic DNA. Additionally, Kolykhalov also teaches that "besides the potential importance of the 3' NTR for HCV replication and recovery of infectious HCV RNA from cDNA, the apparent conservation of the 3' element may have important applications for HCV diagnosis and therapy". The ordinary artisan would have recognized that these two regions were ideal for detecting HCV among numerous isolates. In order to maximize the detection of the number of HCV isolates in a single assay, the skilled artisan would have been motivated to have amplified two regions which were known to detect HCV in a single assay. While the 98-base sequence of the 3' UTR region has demonstrated conservation between isolates of 98-100%, the 3' UTR region of all isolates have not been fully studied. Thus, additionally using conserved regions of the well characterized 5' UTR would have been

an additional control which would detect additional isolates which may not have been previously detected using the 98-base sequence of the 3' UTR region. Secondly, the skilled artisan would have also been motivated to have amplified both the 5' and 3' UTR regions of HCV genome simultaneously in a multiplex reaction to detect HCV for the expected benefit of saving time and reagents. The multiplexing of numerous primers into a single reaction has the express benefit of saving reagent by limiting the number of assays and also saving time of scientists since the results may be obtained simultaneously. Therefore, taking two known regions which were ideal for detecting HCV, as taught by the art, and either detecting the two regions separately or in a multiplex reaction would have been obvious to one of ordinary skill in the art such that numerous isolates which may not be detected by one region or one primer pair would be likely detected with the additional regions.

Response to Arguments

The response traverses the rejection. The response asserts that neither the particular oligonucleotide sequence of this invention nor their use to detect or amplify HCV nucleic acids would have been obvious to one skilled in the art. The response provides Chapter 15.1 from Current Protocols in Molecular Biology as support that primer selection is "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work". This argument has been reviewed but is not convincing because primer selection is routine in the art at the time the invention was made. While this reference does teach that primer selection is the least predictable, the reference specifically provides "to maximize the probability that a given

primer pair will work, pay attention to the following parameters..". Thus, the art provides guidance for the optimization of primers. Design of primer pairs is routine in the art and merely constitutes optimization which is well within the scope of the ordinary artisan. Moreover, specific optimization kits, computer programs and such are provided to aid the artisan in the primer selection.

The response asserts that "at best, given what is taught in Maertens, Han, Kolykhalov, Tanaka and Encke a skilled artisan might only be motivated to try various probes and primers designed from the 5- or 3'-UTR taught in those references". This argument has been reviewed but is not convincing because optimization of primers and primer pairs is routine in the art. The art teaches how to alter the conditions to obtain primer/primer pairs which amplify the target.

Thus for the reasons above and those already of record, the rejection is maintained.

14. Claims 44, 46, 48, 55, 57, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Maertens et al (US Pat. 5,846,704, December 1998) or Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991), in view of either Kolykhalov et al (J. of Virology, Vol 70, No. 6, pg 3363-3371, June 1996) or Tanaka et al (US Pat. 5,837,463, November 17, 1998) and Encke et al (J. of Virological Methods, Vol. 74, pg. 117-121, September 1998) as applied to Claim 27-39 and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Neither Maertens nor Han nor Kolykhalov nor Tanaka nor Encke specifically teach kit which combines probes and primers from both the 5' UTR region and the 3' UTR region for detection of HCV.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of either Maertens or Han and Kolykhalov or Tanaka nor Encke with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Maertens or Han and Kolykhalov or Tanaka nor Encke into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Maertens or Han and Kolykhalov or Tanaka nor Encke deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers included, into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-2, 4-6, 9-12, 43, 45, 54, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maertens et al (US Pat. 5,846,704, December 1998).

Maertens et al (US Pat. 5,846,704, December 8, 1998) teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches primers which have at least 15 contiguous nucleotides from SEQ ID NO: 3 and 4. The inner primers of Maertens denoted as SEQ ID NO: 3 and 4 which overlap at least 15 contiguous nucleotides of the instant SEQ ID NO: 3 and 5/6. Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68)(limitations of Claim 8). Random primers were then added such that cDNA was synthesized (col 24, lines 60-68)(limitations of Claim 2). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10). The PCR product was then subjected to electrophoresis in an agarose gel and ethidium bromide staining (col. 25, lines 14-15)(limitations of Claim 4, 5, 11). Furthermore, strips of immobilized HCV-specific primers developed and hybridized with PCR amplified DNA fragments of the 5' UTR for visualization (col. 25, lines 50-

60)(limitations of Claim 6, 12). Maertens teaches a kit which comprises a set of primers, a set of probes immobilized on a solid substrate, and buffers (col. 20, lines 45-55)(limitations of Claim 43, 45, 54, 56). Maertens provides specific primers for each of the isolates and universal primers which may be used (Table 4 and 5).

SEQ ID NO: 1 of the instant application overlaps SEQ ID NO: 3 of Maertens. Nucleotides 10-30 of the instant application are identical to nucleotides 1-20 of Maertens.

SEQ ID NO: 2 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 17-25 of the instant application are identical to nucleotides 1-9 of Maertens.

SEQ ID NO: 3 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 5-20 of the instant application are identical to nucleotides 1-15 of Maertens.

SEQ ID NO: 4 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 12-1 of the instant application are identical to nucleotides 1-12 of Maertens.

SEQ ID NO: 5 of the instant application overlaps SEQ ID NO: 4 of Maertens. Nucleotides 1-21 of the instant application are identical to nucleotides 6-26 of Maertens.

SEQ ID NO: 6 of the instant application contains all 26 of the nucleotides of SEQ ID NO: 4 of Maertens. SEQ ID NO: 6 would be identical except SEQ ID NO: 6 contains an additional A nucleotide on the 3' end of the oligonucleotide.

SEQ ID NO: 7 of the instant application overlaps SEQ ID NO: 4 of Maertens. Nucleotides 5-25 of the instant application are identical to nucleotides 1-20 of Maertens.

Maertens does not specifically teach the primers of the instant claimed invention.

However, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent structural and functional homologues of the full length disclosed 5' UTR HCV sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method and primers of Maertens to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Maertens. The instant primers overlap the primers of Maertens such that it would be presumed that these primers would have the same properties and amplify the same regions. Moreover, any primers which amplify the 5' UTR region and any probes within the 5' UTR region which detect HCV would have been obvious.

Response to Arguments

The response traverses the rejection. The response asserts that Maertens does not apply as 102 art against the claims. This reference has been reconsidered and applied under 103.

Conclusion

16. No claims allowable over the art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
April 17, 2001 JG

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800-1600